# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Friend et al.

Application No.: To be assigned; Division of
        Serial No. 09/303,082, filed
        April 30, 1999

Group Art Unit: To be assigned

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Examiner: To be assigned

For:   METHODS OF DETERMINING
       PROTEIN ACTIVITY LEVELS USING
       GENE EXPRESSION PROFILES

Attorney Docket No.: 9301-161

## PRELIMINARY AMENDMENT UNDER 37 C.F.R. §1.115

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to 37 C.F.R. § 1.115, please enter the following amendments and remarks in connection with the above-identified application. Applicants submit concurrently herewith: 1) Exhibit A: marked version of the amended claims; 2) Exhibit B: clean version of the pending claims, as amended; 3) Amendment Fee Transmittal (in duplicate), accompanied by the appropriate fee; and 4) Information Disclosure Statement, including revised Form PTO-1449: "List of References Cited by Applicant" and copies of references AA-EW, accompanied by the appropriate fee.

## IN THE CLAIMS:

A marked up version of the claims showing the amendments is attached hereto as Exhibit A. Matter that has been deleted from claims 54, 57-58 and 68 is indicated by brackets and matter that has been added is indicated by underlining. A clean version of the pending claims, as amended, is attached hereto as Exhibit B.

Please amend the claims as follows:

Please amend claims 54, 57-58 and 68 to read as follows:

54. (Amended) The computer system of claim 53 wherein determining the level of perturbation is achieved by a method comprising:

(a)    determining the value of a function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

(b)    minimizing said determined value of said function by varying the level of perturbation to said protein to determine a level of perturbation that minimizes said determined value of said function.

57. (Amended) The computer system of claim 54 wherein said function comprises a sum of the squares of differences of the diagnostic profile and the perturbation response profile extracted from said perturbation response curves.

58. (Amended) The computer system of claim 53 wherein determining the level of perturbation is achieved by a method comprising:

(a)    determining the value of a function of the correlation between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

(b)    maximizing said determined value of said function by varying the level of perturbation to said protein to determine a level of perturbation that maximizes said determined value of said function.

68. (Amended) The computer system of claim 67 wherein said determining the level of perturbation is achieved by a method comprising:

(a)    determining the value of a function of the difference between said diagnostic profile and the combination of the perturbation response profiles extracted from said perturbation response curves for said level of perturbation to each said protein; and

(b)    minimizing said determined value of said function by varying the level of perturbation to each said protein to determine the level of perturbation to each said protein that minimizes said determined value of said function.

Please add new claims as follows:

69. (New) A computer system for measuring activity of a drug *in vivo* comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising

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determining an activity level of a protein in a cell treated with said drug according to a method comprising determining a level of perturbation to said protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for the determined level of perturbation to said protein, wherein:

(a) the diagnostic profile is obtained by a method comprising measuring a first plurality of cellular constituents in the cell treated with said drug; and

(b) the perturbation response curves are provided by a method comprising

(i) providing perturbation response profiles of said protein for a cell, wherein said perturbation response profiles are obtained by a method comprising measuring a second plurality of cellular constituents in a cell at a plurality of discrete levels of perturbation to said protein,

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

and wherein said determined level of perturbation to said protein represents said protein activity level in said cell treated with said drug and said protein activity level is a measure of said drug activity.

70. (New) The computer system of claim 69, wherein determining the level of perturbation is achieved by a method comprising:

(a) determining the value of a function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

(b) minimizing said determined value of said function by varying the level of perturbation to said protein to determine a level of perturbation that minimizes said determined value of said function.

71. (New) A computer system for determining a level of activity of a biologically active cellular constituent of interest comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a level of perturbation to the cellular constituent of interest at which similarity is greatest between a diagnostic profile and

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a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to the cellular constituent of interest,

said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type,

said perturbation response curves being the products of a method comprising:

(i) providing perturbation response profiles of the cellular constituent of interest for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to the cellular constituent of interest, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to the cellular constituent of interest, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to the cellular constituent of interest represents the activity level of said cellular constituent of interest in said cell type.

72. (New) The computer system of claim 71, wherein determining the level of perturbation is achieved by a method comprising:

(a) determining the value of a function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said cellular constituent of interest; and

(b) minimizing said determined value of said function by varying the level of perturbation to said cellular constituent of interest to determine a level of perturbation that minimizes said determined value of said function.

73. (New) A computer system for identifying a cell of a cell type that has one or more genetic mutations or polymorphisms that disrupt activity of one or more corresponding gene products, comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a level of perturbation to each said gene product at which the similarity is greatest between a diagnostic profile and a combination of perturbation response profiles extracted from perturbation response curves for each said gene

product for each said determined level of perturbation, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in said cell, wherein said perturbation response curves for each said gene products are the products of a method comprising

> (i) providing perturbation response profiles of said gene product for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a wild type cell of said cell type at a plurality of discrete levels of perturbation to said gene product, and
> (ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said gene product, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to each said gene product represents the extent to which the activity of said gene product is disrupted, and wherein cells in which corresponding gene product activities are disrupted are identified as having genetic mutations or polymorphisms in said genes.

74. (New) The computer system of claim 73 wherein said determining the level of perturbation is achieved by a method comprising:

(a)     determining the value of a function of the difference between said diagnostic profile and the combination of the perturbation response profiles extracted from said perturbation response curves for said level of perturbation to each said gene product; and

(b)     minimizing said determined value of said function by varying the level of perturbation to each said gene product to determine the level of perturbation to each said gene product that minimizes said determined value of said function.

75. (New) A computer system for determining the dose of one or more drugs to achieve a desired clinical effect in a patient comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a dose of said one or

more drugs where similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein

(a) the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said one or more drugs; and

(b) the perturbation response profile associated with the desired clinical effect is provided by a method comprising

(i) providing a plurality of perturbation response profiles of said one or more drugs for one or more cells of one or more patients, wherein said plurality of perturbation response profiles is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells at a plurality of discrete levels of exposure to said one or more drugs, and

(ii) calibrating said plurality of perturbation response profiles to clinical effects of the one or more drugs,

wherein said determined dose of said one or more drugs where similarity is greatest is the dose of said one or more drugs to achieve said desired clinical effect in said patient.

76. (New) The computer system of claim 75 wherein determining a dose of said one or more drugs is achieved by a method comprising:

(a) determining the value of a function of the difference between said diagnostic profile and the perturbation response profile associated with the desired clinical effect; and

(b) minimizing said determined value of said function by varying the dose of said one or more drugs to determine a dose of said one or more drugs that minimizes said determined value of said function.

77. (New) A computer system for determining a drug therapy to achieve a desired clinical effect in a patient comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a drug therapy where similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein,

(a)    the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said drug therapy; and

(b)    the perturbation response profile associated with the desired clinical effect is provided by a method comprising

   (i)    providing a plurality of perturbation response profiles for a plurality of drug therapies, wherein said plurality of perturbation response profiles is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells for a plurality of drug therapies, and

   (ii)    calibrating said plurality of perturbation response profiles to clinical effects of the plurality of drug therapies,

wherein said determined drug therapy where similarity is greatest is the drug therapy to achieve said desired clinical effect in said patient.

78. (New) The computer system of claim 77 wherein determining the drug therapy is achieved by a method comprising:

(a)    determining the value of a function of the difference between said diagnostic profile and the perturbation response profile associated with the desired clinical effect; and

(b)    minimizing said determined value of said function by varying the dosage of said drug therapy to determine the dosage of said drugs therapy that minimizes said determined value of said function.

79. (New) A computer program product for use in conjunction with a computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a level of perturbation to a protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to a protein, said diagnostic profile having been obtained by

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a method comprising measuring a first plurality of cellular constituents in a cell of said cell type, said perturbation response curves being the products of a method comprising:

(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to said protein represents a level of activity of said protein in said cell type.

80. (New) A computer program product for use in conjunction with a computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining an activity level of a protein in a cell treated with a drug according to a method comprising determining a level of perturbation to said protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for the determined level of perturbation to said protein, wherein:

(a)     the diagnostic profile is obtained by a method comprising measuring a first plurality of cellular constituents in the cell treated with said drug; and

(b)     the perturbation response curves are provided by a method comprising

(i)     providing perturbation response profiles of said protein for a cell, wherein said perturbation response profiles are obtained by a method comprising measuring a second plurality of cellular constituents in a cell at a plurality of discrete levels of perturbation to said protein,

(ii)     interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation

to said protein, wherein said interpolated response profiles comprise
said perturbation response curves,

and wherein said determined level of perturbation to said protein represents said protein activity level in said cell treated with said drug and said protein activity level is a measure of activity of said drug.

81. (New) A computer program product for use in conjunction with a computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a level of perturbation to a biologically active cellular constituent of interest at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to the cellular constituent of interest,

said diagnostic profile having been obtained by a method comprising measuring a first
plurality of cellular constituents in a cell of said cell type,

said perturbation response curves being the products of a method comprising:

(i) providing perturbation response profiles of the cellular constituent of interest for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to the cellular constituent of interest, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to the cellular constituent of interest, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to the cellular constituent of interest represents a level of activity of said cellular constituent of interest in said cell type.

82. (New) A computer program product for use in conjunction with a computer for identifying a cell of a cell type that has one or more genetic mutations or polymorphisms that disrupt activity of one or more corresponding gene products, said computer having a

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processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a level of perturbation to each said gene product at which the similarity is greatest between a diagnostic profile and a combination of perturbation response profiles extracted from perturbation response curves for each said gene product for each said determined level of perturbation, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in said cell, wherein said perturbation response curves for each said gene products are the products of a method comprising

> (i) providing perturbation response profiles of said gene product for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a wild type cell of said cell type at a plurality of discrete levels of perturbation to said gene product, and
> (ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said gene product, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to each said gene product represents the extent to which the activity of said gene product is disrupted, and wherein cells in which corresponding gene product activities are disrupted are identified as having genetic mutations or polymorphisms in said genes.

83. (New) A computer program product for use in conjunction with a computer for determining the dose of one or more drugs to achieve a desired clinical effect in a patient, said computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a dose of said one or more drugs where similarity is greatest between

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a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein

(a)    the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said one or more drugs; and

(b)    the perturbation response profile associated with the desired clinical effect is provided by a method comprising

    (i)    providing a plurality of perturbation response profiles of said one or more drugs for one or more cells of one or more patients, wherein said plurality of perturbation response profiles is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells at a plurality of discrete levels of exposure to said one or more drugs, and

    (ii)    calibrating said plurality of perturbation response profiles to clinical effects of the one or more drugs,

wherein said determined dose of said one or more drugs where similarity is greatest is the dose of said one or more drugs to achieve said desired clinical effect in said patient.

84. (New) A computer program product for use in conjunction with a computer for determining a drug therapy to achieve a desired clinical effect in a patient, said computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a drug therapy where similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein

(a)    the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said drug therapy; and

(b)    the perturbation response profile associated with the desired clinical effect is provided by a method comprising

    (i)    providing a plurality of perturbation response profiles for a plurality of drug therapies, wherein said plurality of perturbation response profiles

is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells for a plurality of drug therapies, and

(ii)     calibrating said plurality of perturbation response profiles to clinical effects of the plurality of drug therapies,

wherein said determined drug therapy where similarity is greatest is the drug therapy to achieve said desired clinical effect in said patient.

## REMARKS

The subject application is a divisional application of application Serial No. 09/303,082 filed on April 30, 1999. Claims 54, 57-58 and 68 have been amended and new claims 69-84 have been added to more particularly point out and distinctly claim the invention. Upon entry of the instant amendment, claims 53-59, 67-84 will be pending. A marked up version of the claims showing the amendments is attached hereto as Exhibit A. A clean version of the pending claims, as amended, is attached hereto as Exhibit B.

Claims 54, 57 and 68 have been amended to more particularly point out that the claimed methods involve determining and minimizing the value of *a function* of the difference between said diagnostic profile and the perturbation response profile (emphasis added). Support for the amendments is found in the specification, e.g., at page 30, line 18 through page 31, line 7.

Claim 58 has been amended to more particularly point out that the claimed method involves determining and *maximizing* the value of a function of *the correlation between said diagnostic profile and the perturbation response profile* extracted from said perturbation response curves for a level of perturbation to said protein (emphasis added). Support for the amendment is found in the specification at page 31, lines 8-31. Claim 58 has also been amended to depend on claim 53.

Support for new claims 69-70 is found in the specification, *e.g.*, at page 36, line 1 through page 38, line 23; and at page 82, line 19 through page 83, line 29. Support for new claims 71-72 is found in the specification, *e.g.*, at page 36, line 1 through page 38, line 23; and at page 7, lines 5-27 and page 13, lines 24-30. Support for new claims 73-74 is found in the specification, *e.g.*, at page 36, line 1 through page 38, line 23; and at page 8, lines 10-34. Support for new claims 75-78 is found in the specification, *e.g.*, at page 36, line 1 through page 38, line 23; at page 9, lines 17-34; and at page 85, lines 8-20. Support for new claim 79

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is found in the specification at page 37, lines 19-25 and page 39, lines 12-20; and at page 7, lines 5-27. Support for new claim 80 is found in the specification at page 37, lines 19-25 and page 39, lines 12-20; and at page 82, line 19 through page 83, line 29. Support for new claim 81 is found in the specification at page 37, lines 19-25 and page 39, lines 12-20; and at page 7, lines 5-27 and page 13, lines 24-30. Support for new claim 82 is found in the specification at page 37, lines 19-25 and page 39, lines 12-20; and at page 8, lines 10-34. Support for new claim 83-84 is found in the specification at page 37, lines 19-25 and page 39, lines 12-20; and at page 9, lines 17-34; and at page 85, lines 8-20.

No new matter has been added. Entry of the foregoing amendments and remarks is respectfully requested.

## CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application.

Respectfully submitted,

Date      October 12, 2001

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Enclosures

(As amended October 12, 2001)

54. (Amended) The computer system of claim 53 wherein determining the level of perturbation is achieved by a method comprising:

(a)    determining the value of [an objective] a function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

(b)    minimizing said determined value of said [objective] function by varying the level of perturbation to said protein to determine a level of perturbation that minimizes said determined value of said [objective] function.

57. (Amended) The computer system of claim 54 wherein said [objective] function comprises a sum of the squares of differences of the diagnostic profile and the perturbation response profile extracted from said perturbation response curves.

58. (Amended) The computer system of claim [54] 53 [wherein said objective function comprises the negative of the correlation of the diagnostic profile and the perturbation response profile extracted from said perturbation response curves] wherein determining the level of perturbation is achieved by a method comprising:

(a)    determining the value of a function of the correlation between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

(b)    maximizing said determined value of said function by varying the level of perturbation to said protein to determine a level of perturbation that maximizes said determined value of said function.

68. (Amended) The computer system of claim 67 wherein said determining the level of perturbation is achieved by a method comprising:

(a)    determining the value of [an objective] a function of the difference between said diagnostic profile and the combination of the perturbation response profiles

extracted from said perturbation response curves for said level of perturbation to each said protein; and

(b)      minimizing said determined value of said [objective] function by varying the level of perturbation to each said protein to determine the level of perturbation to each said protein that minimizes said determined value of said [objective] function.

New claims 69-84 have been added.

**EXHIBIT B: CLEAN VERSION OF THE PENDING CLAIMS**
U.S. PATENT APPLICATION SERIAL NO. To be assigned
(ATTORNEY DOCKET NO. 9301-161)

(As amended October 12, 2001)

53. A computer system for determining a level of protein activity comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a level of perturbation to said protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to said protein, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type, said perturbation response curves being the products of a method comprising:

(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to said protein represents said protein activity level in said cell type.

54. (Amended) The computer system of claim 53 wherein determining the level of perturbation is achieved by a method comprising:

(a)      determining the value of a function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

(b)      minimizing said determined value of said function by varying the level of perturbation to said protein to determine a level of perturbation that minimizes said determined value of said function.

55. The computer system of claim 53 wherein said diagnostic profiles and said perturbation response curves are made available in said memory.

56. The computer system of claim 55 wherein said programs cause said processor to perform said step of interpolating said perturbation response profiles.

57. (Amended) The computer system of claim 54 wherein said function comprises a sum of the squares of differences of the diagnostic profile and the perturbation response profile extracted from said perturbation response curves.

58. (Amended) The computer system of claim 53 wherein determining the level of perturbation is achieved by a method comprising:

   (a)   determining the value of a function of the correlation between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

   (b)   maximizing said determined value of said function by varying the level of perturbation to said protein to determine a level of perturbation that maximizes said determined value of said function.

59. The computer system of claim 54 wherein said minimizing comprises performing the Levenberg-Marquandt method.

67. A computer system for determining levels of protein activity comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a level of perturbation to each said protein at which similarity is greatest between a diagnostic profile and a combination of perturbation response profiles extracted from perturbation response curves for each said protein for each said determined level of perturbation, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type, wherein said perturbation response curves for each of said proteins are the products of a method comprising

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(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves

wherein said determined level of perturbation to each said protein represents said activity level of each said protein in said cell type.

68. (Amended) The computer system of claim 67 wherein said determining the level of perturbation is achieved by a method comprising:

(a)    determining the value of a function of the difference between said diagnostic profile and the combination of the perturbation response profiles extracted from said perturbation response curves for said level of perturbation to each said protein; and

(b)    minimizing said determined value of said function by varying the level of perturbation to each said protein to determine the level of perturbation to each said protein that minimizes said determined value of said function.

69. (New) A computer system for measuring activity of a drug *in vivo* comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining an activity level of a protein in a cell treated with said drug according to a method comprising determining a level of perturbation to said protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for the determined level of perturbation to said protein, wherein:

(a)    the diagnostic profile is obtained by a method comprising measuring a first plurality of cellular constituents in the cell treated with said drug; and

(b)    the perturbation response curves are provided by a method comprising

(i)    providing perturbation response profiles of said protein for a cell, wherein said perturbation response profiles are obtained by a method

comprising measuring a second plurality of cellular constituents in a cell at a plurality of discrete levels of perturbation to said protein,

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

and wherein said determined level of perturbation to said protein represents said protein activity level in said cell treated with said drug and said protein activity level is a measure of said drug activity.

70. (New) The computer system of claim 69, wherein determining the level of perturbation is achieved by a method comprising:

(a) determining the value of a function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said protein; and

(b) minimizing said determined value of said function by varying the level of perturbation to said protein to determine a level of perturbation that minimizes said determined value of said function.

71. (New) A computer system for determining a level of activity of a biologically active cellular constituent of interest comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a level of perturbation to the cellular constituent of interest at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to the cellular constituent of interest,

said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type,

said perturbation response curves being the products of a method comprising:

(i) providing perturbation response profiles of the cellular constituent of interest for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in

a cell of said cell type at a plurality of discrete levels of perturbation to the cellular constituent of interest, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to the cellular constituent of interest, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to the cellular constituent of interest represents the activity level of said cellular constituent of interest in said cell type.

72. (New) The computer system of claim 71, wherein determining the level of perturbation is achieved by a method comprising:

(a) determining the value of a function of the difference between said diagnostic profile and the perturbation response profile extracted from said perturbation response curves for a level of perturbation to said cellular constituent of interest; and

(b) minimizing said determined value of said function by varying the level of perturbation to said cellular constituent of interest to determine a level of perturbation that minimizes said determined value of said function.

73. (New) A computer system for identifying a cell of a cell type that has one or more genetic mutations or polymorphisms that disrupt activity of one or more corresponding gene products, comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a level of perturbation to each said gene product at which the similarity is greatest between a diagnostic profile and a combination of perturbation response profiles extracted from perturbation response curves for each said gene product for each said determined level of perturbation, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in said cell, wherein said perturbation response curves for each said gene products are the products of a method comprising

(i) providing perturbation response profiles of said gene product for said cell type, wherein said perturbation response profiles are obtained by measuring a

second plurality of cellular constituents in a wild type cell of said cell type at a plurality of discrete levels of perturbation to said gene product, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said gene product, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to each said gene product represents the extent to which the activity of said gene product is disrupted, and wherein cells in which corresponding gene product activities are disrupted are identified as having genetic mutations or polymorphisms in said genes.

74. (New) The computer system of claim 73 wherein said determining the level of perturbation is achieved by a method comprising:

(a)     determining the value of a function of the difference between said diagnostic profile and the combination of the perturbation response profiles extracted from said perturbation response curves for said level of perturbation to each said gene product; and

(b)     minimizing said determined value of said function by varying the level of perturbation to each said gene product to determine the level of perturbation to each said gene product that minimizes said determined value of said function.

75. (New) A computer system for determining the dose of one or more drugs to achieve a desired clinical effect in a patient comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a dose of said one or more drugs where similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein

(a)     the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said one or more drugs; and

(b)     the perturbation response profile associated with the desired clinical effect is provided by a method comprising

(i) providing a plurality of perturbation response profiles of said one or more drugs for one or more cells of one or more patients, wherein said plurality of perturbation response profiles is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells at a plurality of discrete levels of exposure to said one or more drugs, and

(ii) calibrating said plurality of perturbation response profiles to clinical effects of the one or more drugs,

wherein said determined dose of said one or more drugs where similarity is greatest is the dose of said one or more drugs to achieve said desired clinical effect in said patient.

76. (New) The computer system of claim 75 wherein determining a dose of said one or more drugs is achieved by a method comprising:

(a) determining the value of a function of the difference between said diagnostic profile and the perturbation response profile associated with the desired clinical effect; and

(b) minimizing said determined value of said function by varying the dose of said one or more drugs to determine a dose of said one or more drugs that minimizes said determined value of said function.

77. (New) A computer system for determining a drug therapy to achieve a desired clinical effect in a patient comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising determining a drug therapy where similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein,

(a) the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said drug therapy; and

(b) the perturbation response profile associated with the desired clinical effect is provided by a method comprising

(i) providing a plurality of perturbation response profiles for a plurality of drug therapies, wherein said plurality of perturbation response profiles

is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells for a plurality of drug therapies, and

(ii)     calibrating said plurality of perturbation response profiles to clinical effects of the plurality of drug therapies,

wherein said determined drug therapy where similarity is greatest is the drug therapy to achieve said desired clinical effect in said patient.


78. (New) The computer system of claim 77 wherein determining the drug therapy is achieved by a method comprising:

(a)     determining the value of a function of the difference between said diagnostic profile and the perturbation response profile associated with the desired clinical effect; and

(b)     minimizing said determined value of said function by varying the dosage of said drug therapy to determine the dosage of said drugs therapy that minimizes said determined value of said function.


79. (New) A computer program product for use in conjunction with a computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a level of perturbation to a protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to a protein, said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type, said perturbation response curves being the products of a method comprising:

(i) providing perturbation response profiles of said protein for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to said protein, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to said protein represents a level of activity of said protein in said cell type.

80. (New) A computer program product for use in conjunction with a computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining an activity level of a protein in a cell treated with a drug according to a method comprising determining a level of perturbation to said protein at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for the determined level of perturbation to said protein, wherein:

    (a)    the diagnostic profile is obtained by a method comprising measuring a first plurality of cellular constituents in the cell treated with said drug; and

    (b)    the perturbation response curves are provided by a method comprising

        (i)    providing perturbation response profiles of said protein for a cell, wherein said perturbation response profiles are obtained by a method comprising measuring a second plurality of cellular constituents in a cell at a plurality of discrete levels of perturbation to said protein,

        (ii)    interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said protein, wherein said interpolated response profiles comprise said perturbation response curves,

and wherein said determined level of perturbation to said protein represents said protein activity level in said cell treated with said drug and said protein activity level is a measure of activity of said drug.

81. (New) A computer program product for use in conjunction with a computer having a processor and a memory connected to the processor, said computer program product

comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a level of perturbation to a biologically active cellular constituent of interest at which similarity is greatest between a diagnostic profile and a perturbation response profile extracted from perturbation response curves for said determined level of perturbation to the cellular constituent of interest,

        said diagnostic profile having been obtained by a method comprising measuring a first plurality of cellular constituents in a cell of said cell type,

    said perturbation response curves being the products of a method comprising:

(i)     providing perturbation response profiles of the cellular constituent of interest for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a cell of said cell type at a plurality of discrete levels of perturbation to the cellular constituent of interest, and

(ii)    interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to the cellular constituent of interest, wherein said interpolated response profiles comprise said perturbation response curves,

    wherein said determined level of perturbation to the cellular constituent of interest represents a level of activity of said cellular constituent of interest in said cell type.


82. (New) A computer program product for use in conjunction with a computer for identifying a cell of a cell type that has one or more genetic mutations or polymorphisms that disrupt activity of one or more corresponding gene products, said computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a level of perturbation to each said gene product at which the similarity is greatest between a diagnostic profile and a combination of perturbation response profiles extracted from perturbation response curves for each said gene product for each said determined level of perturbation, said diagnostic profile having been obtained by a method comprising measuring

a first plurality of cellular constituents in said cell, wherein said perturbation response curves for each said gene products are the products of a method comprising

(i) providing perturbation response profiles of said gene product for said cell type, wherein said perturbation response profiles are obtained by measuring a second plurality of cellular constituents in a wild type cell of said cell type at a plurality of discrete levels of perturbation to said gene product, and

(ii) interpolating said perturbation response profiles so that a perturbation response profile may be extracted over a range of levels of perturbation to said gene product, wherein said interpolated response profiles comprise said perturbation response curves,

wherein said determined level of perturbation to each said gene product represents the extent to which the activity of said gene product is disrupted, and wherein cells in which corresponding gene product activities are disrupted are identified as having genetic mutations or polymorphisms in said genes.

83. (New) A computer program product for use in conjunction with a computer for determining the dose of one or more drugs to achieve a desired clinical effect in a patient, said computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a dose of said one or more drugs where similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein

(a)     the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said one or more drugs; and

(b)     the perturbation response profile associated with the desired clinical effect is provided by a method comprising

(i)     providing a plurality of perturbation response profiles of said one or more drugs for one or more cells of one or more patients, wherein said

plurality of perturbation response profiles is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells at a plurality of discrete levels of exposure to said one or more drugs, and

(ii) calibrating said plurality of perturbation response profiles to clinical effects of the one or more drugs,

wherein said determined dose of said one or more drugs where similarity is greatest is the dose of said one or more drugs to achieve said desired clinical effect in said patient.


84. (New) A computer program product for use in conjunction with a computer for determining a drug therapy to achieve a desired clinical effect in a patient, said computer having a processor and a memory connected to the processor, said computer program product comprising a computer readable storage medium having a computer program mechanism encoded thereon, wherein said computer program mechanism may be loaded into the memory of said computer and cause said computer to carry out a method comprising determining a drug therapy where similarity is greatest between a diagnostic profile and a perturbation response profile associated with the desired clinical effect, wherein

(a) the diagnostic profile is provided by a method comprising measuring a first plurality of cellular constituents in one or more cells from said patient treated with said drug therapy; and

(b) the perturbation response profile associated with the desired clinical effect is provided by a method comprising

(i) providing a plurality of perturbation response profiles for a plurality of drug therapies, wherein said plurality of perturbation response profiles is obtained by a method comprising measuring a second plurality of cellular constituents in one or more cells for a plurality of drug therapies, and

(ii) calibrating said plurality of perturbation response profiles to clinical effects of the plurality of drug therapies,

wherein said determined drug therapy where similarity is greatest is the drug therapy to achieve said desired clinical effect in said patient.